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EXAMINER	
BAUGHMAN, MOLLY E	

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1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,980	LEE ET AL.	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-83,85 and 86* is/are pending in the application.

4a) Of the above claim(s) *72-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-71,85 and 86* is/are rejected.

7)☒ Claim(s) *71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/31/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' amendments to claims 45, 59, and 65 in the reply filed on 10/24/08 are acknowledged.

2. Claims 43-83 and 85-86 are currently pending; claims 72-83 remain withdrawn, and claims 43-71 and 85-86 are currently under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 12/31/08 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, some citations have been either modified, or lined through for the following reasons:

a. The Office Actions corresponding to U.S. Applications submitted in the information disclosure statements (IDS) have been fully considered, although, they have been lined through as they are not appropriate documents for printed patents. Please be advised that applicants are able to list the U.S. Pre-Grant Publication numbers associated with such applications under the U.S. Patents section of the IDS.

b. The citation, Lee et al. (US 6,833,257) has been lined through in order to avoid duplicate references at time of print (already cited by Examiner on 9/28/07).

Response to Arguments

4. Applicant's arguments, see pg.3, filed 10/24/08, with respect to rejection of claim 86 under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The rejection of claim 86 has been withdrawn.

5. Applicant's arguments, see pg.1-11, filed 10/24/08, with respect to the following rejection(s):

c. Claim(s) 43-44, 48-55, and 57-69 rejected under 35 USC § 102(e), Lee (US 2004/0241679, priority date 5/25/01).

d. Claim(s) 43-44 and 48-69 rejected under nonstatutory obvious-type double patenting over claims 1-4, 6-7, 9, and 10-14 of copending application 10/478,788.

e. Claims 43-44 and 48-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (WO/99/28500, of record).

f. Claims 45-47, 66-71, and 85-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO/99/28500, of record) in view of Smith et al., "Mitoxantrone-DNA binding and the induction of Topoisomerase II associated DNA Damage in Multi-drug resistant small cell lung cancer cells," Biochem. Pharma. 1990, Vol.40, No.9, pp.2069-2078.

g. Claims 45-47, 66-71, and 85-86 are rejected under 35 U.S.C. 103(a) as being obvious over Lee (US 2004/0241679, priority date 5/25/01), in view of Smith et al., "Mitoxantrone-DNA binding and the induction of Topoisomerase II associated DNA Damage in Multi-drug resistant small cell lung cancer cells," Biochem. Pharma. 1990, Vol.40, No.9, pp.2069-2078.

h. Claims 43-46, and 48-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-9, 11-13 are of U.S. Patent No. 6,833,257 in view of Smith et al., "Mitoxantrone-DNA binding and the induction of Topoisomerase II associated DNA Damage in Multi-drug resistant small cell lung cancer cells," Biochem. Pharma. 1990, Vol.40, No.9, pp.2069-2078.

have been fully considered and are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection have been made below.

New Grounds of Rejection

Claim Objections

6. Claim 71 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim *should refer to other claims in the alternative only*. See MPEP § 608.01(n). Accordingly, the claim 71 has not been further treated on the merits.

Claim Rejections - 35 USC § 112

First Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

8. Claims 43-70, and 85-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Independent claims 43 and 66 are drawn to methods which comprise the use of any DNA duplex binding agent which is able to absorb fluorescence from a fluorescent label on a probe, and where its emissions are not detectable in the context of the method.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The specification discloses theoretical DNA duplex binding agents which may emit radiation at wavelengths outside the visible range of the spectrum (pg.4, lines 27-37) and theoretical DNA binding agents having such properties which have conjugated aromatic ring systems (see pg.5, lines 8-16). However, the specification only discloses the particular structure identified as formula (I) (pg.5), comprising various functional

groups and substituents (pg.5-6). Additionally, the applicants do not have any support to whether any compounds represented by this formula will in fact act as a fluorescence absorber and not have detectable emissions in the context of the method, let alone even act as a DNA duplex binding agent. The specification even supports this on pg.7 as it states, "Compounds which may be suitable for use as DNA duplex binding agents in the invention may be tested to see whether or not they absorb fluorescent energy for example, from a particular or from a range of labels using conventional methods." Applicants only provide a number of particular compounds listed on the bottom of pg.7 through pg.8. The examples only provide mitoxantrone used in the manner of the method being claimed, and Figure 5 only demonstrates mitoxantrone and daunomycin being analyzed. Example 3 provides a method of identifying further DNA duplex binding agents which are able to perform in this manner, however, it does not list any particular compounds and only provides a theoretical procedure for identifying further DNA duplex binding agents which absorb fluorescent energy and can act as a "dark quencher."

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides examples of only mitoxantrone and daunomycin being used in the manner of the method, and it is entirely unpredictable whether any other compounds which have a similar formula would behave in a similar fashion. The independent claims encompass any DNA duplex binding agent which can behave in this manner and this is an enormous genus of DNA duplex binding agents.

The dependent claims 47 and 71 encompass any DNA binding agent represented by the compound in formula (I), which is a huge genus and as stated above, it is unpredictable whether all compounds in this genus would behave as a DNA binding agent, fluorescence absorber, and/or have emissions which are not detectable in the context of the method (or do not emit visible light).

In the instant application, the provided information does not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of a compound represented by formula (I). Adequate written description requires more than a statement that any DNA duplex binding agent is able to perform in the manner being claimed. Actual demonstration that each compound is able to bind to a DNA duplex, absorb fluorescence, and have emissions which are not detectable in the context of the method (or do not emit visible light) is required.

In conclusion, the limited information provided is not deemed sufficient to reasonably convey to one skilled in the art the DNA duplex binding agents claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Scope of Enablement

9. Claims 43-70 and 85-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the DNA binding agent being

mitoxantrone and daunomycin, does not reasonably provide enablement for any other DNA duplex binding agents, including any others represented by formula (I). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are broadly drawn to methods comprising a DNA duplex binding agent which can absorb fluorescent energy from a fluorescent label, but does not have emissions which are detectable in the context of the method (or as in claims 85-86, does not emit visible light), which encompasses any agent which can bind to DNA, absorb fluorescent energy from a fluorescent label, and either not have emissions which

are detectable in context of the method (i.e. claims 43-70) , or not emit visible light (i.e. claims 85-86). Dependent claims encompass particular DNA duplex binding agents comprising mitoxantrone, or its salt, nogalamycin, or daunomycin (i.e. claims 45-46, and 70), as well any DNA duplex binding agent represented by formula (I) (i.e. claim 47). This encompasses an enormous genus of DNA duplex binding agents, where it is entirely unpredictable whether any of said compounds are capable of such characteristics required by the claims.

Quantity of Experimentation

The quantity of experimentation in this area is immense since it would require obtaining a plethora of DNA duplex binding agents, including all represented by the formula according to formula (I), and testing each one for its ability to bind to DNA, absorb fluorescence from various fluorescent labels, and determining its emission range. The specification even supports this on pg.7, where it discusses that such compounds suitable will be tested to see whether or not they absorb fluorescent energy from a particular or from a range of labels, and it further explains that such compounds need to be tested to ensure that they also do not impede the progress of the amplification itself. Therefore, each would need to be tested during various amplification conditions as well. Example 3 provides a basic outline in order to identify further quenching DNA binding agents. In summary, this would require a great deal of experimentation.

The unpredictability of the art and the state of the prior art

First, in a broader sense, the art teaches that it is entirely unpredictable whether a DNA duplex binding agent is able to absorb energy from a fluorescent donor in similar methods. Didenko et al., [i.e. Didenko et al., "DNA Probes Using Fluorescence Resonance Energy Transfer (FRET): Designs and Applications," Biotechniques, 2001, Vol.31, No.5, pp.1106-1121], discusses on pg.6 the state of the art involving reactions with hybridization probes in combination with an intercalator and describes DNA duplex binding agent, acridine orange, as a fluorescence *donor* to fluorescent label, rhodamine. Lee et al. [i.e. Lee et al., "ResonSense®: simple linear fluorescent probes for quantitative homogeneous rapid polymerase chain reaction," Analytica Chimica Acta, 2002, pp.61-70], on pg.63, second column, last paragraph, discusses experiments where SYBR® Gold is a *donor* DNA duplex binding agent and fluorescent labels, CY5 and CY5.5 are acceptor agents. In contrast, Lee et al., WO/99/28500, of record, and Fisher et al. (US 5,491,063, of record), describe the use of a different DNA duplex binding agent, ethidium bromide, in similar methods, which is able to absorb fluorescence from a fluorescent label and act as the *acceptor* (see Fisher, abstract and Figures; and Lee pg.11, lines 11-22).

Second, it is entirely unpredictable whether the DNA duplex binding agents which are able to absorb energy from a fluorescent label will have emissions that are either (1) not detectable in the context of the method, or (2) or not in the visible range of the spectrum. Lee et al., WO/99/28500, of record, and Fisher et al. (US 5,491,063, of record), describe the use of ethidium bromide, wherein its emissions are not detectable

in the context of the method (see Fisher col.4, lines 44-50; and col.5, lines 16-25; and Figs. 1 and 3; and Lee pg.7, lines 1-5; and pg.11, lines 11-22), however, ethidium bromide's emissions (if are being measured) are within the visible range of the spectrum.

Third, in a narrower context, it is entirely unpredictable whether any compounds represented by formula (I), other than mitoxantrone and daunomycin, will be able to (1) be a DNA duplex binding agent, (2), be a fluorescence absorber, and/or (3) have emissions which are either not detectable in the context of the method or not in the visible range of the spectrum. This is consistent with the specification as it states on pg.7, "compounds which may be suitable for use as DNA duplex binding agents in the invention may be tested to see whether or not they absorb fluorescent energy...a suitable protocol for carrying out this testing is set out in Example 3 hereinafter" (col.7, lines 23-33). The specification only describes mitoxantrone and daunomycin as DNA duplex binding agents which have such characteristics. It describes other compounds of formula (I) as described in US Patent 5,132,327, and US 5,132,327 only describes these compounds as anti-cancer compounds. There is no description in this patent whether all compounds represented by this formula are able to bind DNA, or absorb fluorescence, and there is no discussion regarding their emissions. The art only describes daunomycin and mitoxantrone as DNA duplex binding agents according to formula (I) which are able to absorb energy emissions. Marrazza et al., [Biosens. and Bioelect., 1999 (of record)], discusses daunomycin absorbing electrochemical energy, however, it is silent to whether it is able to absorb emissions from a fluorescent label

(see Fig.2). Yun et al. (US 7,090,977, of record) discusses nogalamycin and mitoxantrone as intercalators able to absorb electrical energy from ruthenium complexes, however, it is silent to whether either of these absorbing emissions from a fluorescent label (see Fig.1; col.1, lines 61-67; col.2, lines 1-14; and col.5, lines 48-53). Lastly, Smith et al. [Biochem. Pharma. 1990, of record] describe mitoxantrone as a compound able to absorb emissions from a fluorescent label (see Figure 7a and b; pg.2071, "Flow cyotmetric analysis of mitoxantrone-DNA interaction by Ho33342-DNA," and pg.2075, left column).

Working Examples

The specification only has working examples involving daunomycin and mitoxantrone as DNA duplex binding agents which are able to (1) be a DNA duplex binding agent, (2), be a fluorescence absorber, and/or (3) have emissions which are either not detectable in the context of the method or not in the visible range of the spectrum (see Examples 1 and 2 which only use mitoxantrone; and Figs.4-5 which comprises data from daunomycin and mitoxantrone). Examples 3-6 describes a protocol to be used to identify further DNA duplex binding agents. It also lists mitoxantrone, daunomycin, Draq5™, and Apoptrak™ as useful DNA duplex binding agents, however, it supplies no data for Draq5™, and Apoptrak™.

Guidance in the Specification.

The specification provides no guidance on whether any compound represented by formula (I) or any other DNA duplex binding agent for that matter, will be (1) be a DNA duplex binding agent, (2), a fluorescence absorber, and/or (3) have emissions which are either not detectable in the context of the method or not in the visible range of the spectrum. The specification describes compounds of formula (I) according to those listed in US Patent 5,132,327, and US 5,132,327 only describes these compounds as anti-cancer compounds. There is no description in this patent whether all compounds represented by this formula are able to bind DNA, or absorb fluorescence, and there is no discussion regarding their emissions. The specification also states on pg.7, "compounds which may be suitable for use as DNA duplex binding agents in the invention may be tested to see whether or not they absorb fluorescent energy...a suitable protocol for carrying out this testing is set out in Example 3 hereinafter" (col.7, lines 23-33). At the end of Example 6, it states that the applicants have found that mitoxantrone, daunomycin, Draq5™, and Apoptrak™ are as useful DNA duplex binding agents, however, it supplies no data for Draq5™, and Apoptrak™. Therefore, the specification only describes that it can be contemplated that other compounds having the formula of formula (I) might possess such characteristics, and only tested and confirmed a limited number.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the high as the art teaches it entirely unpredictable whether *any DNA duplex binding agent* will be able to absorb fluorescent energy from various fluorescent labels and either have emissions which are either not detectable in the context of the method or not in the visible range of the spectrum, let alone every compound represented by the formula according to formula (I). The quantity of experimentation to determine such DNA duplex binding agents which would qualify under such limitations is immense and the specification does not provide any guidance to other compounds which meet this criteria other than daunomycin, and mitoxantrone. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the absence of a working examples other than those involving daunomycin, and mitoxantrone, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Second Paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 43-70, and 85-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i. Claims 43-70 and 85-86 are indefinite because it cannot be determined what is encompassed by "wherein emissions from the DNA duplex binding agent are not detectable in the context of the method," in claims 43, 59, and 66. The specification does not describe what "the context of the method" is and therefore, this renders the phrase unclear. Furthermore, the specification only discusses that the DNA duplex binding agent does not emit visible light, or that it does not emit radiation in the visible range of the spectrum. Therefore, this makes it more unclear what is meant by its emissions not being detectable in the context of the method. Clarification is required.

Claim Interpretation

Initially, it is noted that MPEP 2111 states that, " During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. In re Morris, 12'7 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); In re Prater, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969)." As such, for the purposes of examination, it is submitted that the phrase -- wherein emissions from the DNA duplex binding agent are not detectable in the context of the method --, without an express definition of the terms, will be interpreted as a DNA duplex binding agent which may have detectable emissions, but such emissions are not being relied upon for

quantification and detection in the method. Such an interpretation is consistent with the specification, which describes in several instances measuring fluorescence from only the fluorescent label as a means for detection (see pg.3, lines 4-21, where it discusses the emissions of the donor and acceptor being sharp peaks and although it discusses using the acceptor's emission to normalize the signals from the donor and acceptor due to "leakage," the signal being relied upon for detection is the fluorescent label (i.e. donor); and pg.11, lines 14-37, where it discusses only measuring fluorescence from the fluorescent label (donor) for detection).

Additionally, the phrase --a DNA duplex binding agent which *can* absorb fluorescent energy from the fluorescent label on the probe-- (emphasis added) will be interpreted as a DNA duplex binding agent, which can potentially absorb the fluorescent energy but does not necessarily during the method.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 43-45, 47-55, 59-70, and 85-86 are rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et al. (US 5,491,063, of record).

Regarding claim 43, Fisher et al. teach a method for detecting the presence of a target nucleic acid sequence in a sample, said method comprising: (a) adding to a sample suspected of containing said target nucleic acid sequence, a fluorescently labelled probe specific for said target sequence, and a DNA duplex binding agent which can absorb fluorescent energy from the fluorescent label on the probe, wherein emission from the DNA duplex binding agent are not detectable in the context of the method (see col.4, lines 44-50; and col.5, lines 16-25) (b) subjecting the thus formed mixture to all amplification reaction in which target nucleic acid is amplified (see col.5, lines 13-34; col.11, lines 30-35), (c) subjecting said sample to conditions under which the said probe hybridizes to the target sequence (col.4, lines 53-55; col.5, lines 26-29), and (d) monitoring fluorescence from the fluorescent label on the probe (see col.5, lines 15-34 - steps (b) and (d-e); Fig.1 where it demonstrates only measuring fluorescence from the fluorescent label during the method (i.e. the acceptor's emissions are not detectable in the context of the method); Fig.3 which demonstrates that ethidium bromide causes a decrease in fluorescence from the fluorescent labels (i.e. it is capable of absorbing fluorescent energy from the label)).

Regarding claim 44, Fisher teaches DNA duplex binding agents having a fused conjugated ring system (see col.9, lines 11-32 for several agents having fused conjugated ring systems - particularly, ethidium bromide and daunomycin).

Regarding claims 45 and 47, Fisher teaches the DNA duplex binding agent being daunomycin (see col.9, line 27, which is a compound with the formula according to formula (I)).

Regarding claim 48, Fisher teaches the method according to claim 43 wherein the target nucleic acid is rendered single stranded prior to hybridization to the probe in step (c) (see col.11-12, where it discusses PCR; col.16, lines 5-10 where it discusses PCR cycling).

Regarding claim 49, Fisher teaches the method wherein the amplification reaction is the polymerase chain reaction (PCR) (see col.11-12, where it discusses PCR; col.16, lines 5-10 where it discusses PCR cycling)

Regarding claim 50 and 51, Fisher teaches the method wherein the probe hybridizes with the target nucleic acid during every cycle of the amplification reaction and wherein the fluorescence from the sample is monitored throughout the amplification reaction (see Example 4 and col.17, lines 3-20).

Regarding claim 52 and 53, Fisher teaches the method wherein fluorescence data generated is used to determine the rates of probe hybridization and where the fluorescence data is used to quantitate the amount of target nucleic acid present in the sample (see Analysis using a spectrofluorometer in col.16-17).

Regarding claims 54-55, Fisher teaches the method wherein the fluorescent label is a rhodamine dye, Cy5, fluorescein or a fluorescein derivative and wherein the fluorescent label is attached at an end region of the probe (see col.15, lines 27-28 for example and col.8, lines 63-67 thru col.9).

Regarding claim 59, Fisher teaches a method according to claim 43 which comprises performing nucleic acid amplification on a target polynucleotide in the presence of (a) a nucleic acid polymerase (b) at least one primer capable of hybridizing

to said target polynucleotide, (c) an oligonucleotide probe which is capable of binding to said target polynucleotide sequence and which contains a fluorescent label (see Fisher, Example 4 for components (a-c)) and (d) a DNA duplex binding agent which is capable of absorbing fluorescent energy from the said fluorescent label, wherein emissions of the DNA duplex binding agent are not detectable in the context of the method; and monitoring changes in fluorescence during the amplification reaction (see Fig.1 where it demonstrates only measuring fluorescence from the fluorescent label during the method (i.e. the donor's emissions are not detectable in the context of the method); Fig.3 which demonstrates that ethidium bromide causes a decrease in fluorescence from the fluorescent labels (i.e. it is capable of absorbing fluorescent energy from the label); and col.5, lines 25-34).

Regarding claim 60, Fisher teaches the method wherein the amplification is suitably carried out using a pair of amplification primers (see Example 4, col.15).

Regarding claim 61, Fisher teaches the method wherein the nucleic acid polymerase is a thermostable polymerase (see Example 4, Taq polymerase).

Regarding claims 62-65, Fisher teaches the method wherein in a further step, a hybridisation assay is carried out and a hybridization condition which is characteristic of the sequence is measured [i.e. claim 62], wherein the condition is temperature, electrochemical potential, or reaction with an enzyme or chemical [i.e. claim 63-64], and wherein the method is used to detect allelic variation or a polymorphism in a target sequence [i.e. claim 65] (see col.13-14, Examples 2 and 3).

Regarding claim 66, Fisher teaches a method comprising a) adding to a sample suspected of containing said sequence, a fluorescently labeled probe specific for said target sequence and a DNA duplex binding agent able to absorb fluorescence from a fluorescent label on the probe wherein emissions from the DNA duplex binding agent are not detectable in the context of the method (see col.4, lines 44-50; and col.5, lines 16-25), (b) subjecting said sample to conditions under which the said probe hybridizes to the target sequence (col.4, lines 53-55; col.5, lines 26-29), (c) monitoring fluorescence from said sample and determining a particular reaction condition, characteristic of said sequence, at which fluorescence changes as a result of the hybridization of the probe to the sample or destabilization of the duplex formed between the probe and the target nucleic acid sequence (see Fig.1 where it demonstrates only measuring fluorescence from the fluorescent label during the method (i.e. the donor's emissions are not detectable in the context of the method); Fig.3 which demonstrates that ethidium bromide causes a decrease in fluorescence from the fluorescent labels (i.e. it is capable of absorbing fluorescent energy from the label); and col.13-14, Examples 2 and 3 for determining a particular reaction condition).

Regarding claims 67-69, Fisher teaches a method wherein the reaction condition characteristic of said sequence is temperature, electrochemical potential, or reaction with an enzyme or chemical, and wherein the results obtained from two sequences are compared in order to determine the presence of polymorphisms or variations therebetween (see col.13-14, Examples 2 and 3 for determining a particular reaction condition - temperature; and col.11 lines 60-65 where it discusses using the method to

conduct genetic analysis such as screening for sickle cell anemia (which is known to be related a SNP in the beta-globin gene).

Regarding claim 70, Fisher teaches the method wherein the DNA duplex binding agent being daunomycin (see col.9, line 27, which is a compound with the formula according to formula (I)).

Regarding claims 85-86, Fisher teaches the method wherein the DNA duplex binding agent being daunomycin, which inherently does not emit visible light (see col.9, line 27).

14. Claims 43-44 and 48-69 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (WO/99/28500, of record).

Regarding claim 43, Lee et al. teach a method for detecting the presence of a target nucleic acid sequence in a sample, said method comprising: (a) adding to a sample suspected of containing said target nucleic acid sequence, a fluorescently labeled probe specific for said target sequence, and a DNA duplex binding agent which can absorb fluorescent energy from the fluorescent label on the probe, wherein emission from the DNA duplex binding agent are not detectable in the context of the method (b) subjecting the thus formed mixture to all amplification reaction in which target nucleic acid is amplified, (c) subjecting said sample to conditions under which the said probe hybridizes to the target sequence, and (d) monitoring fluorescence from the fluorescent label on the probe

(Lee teaches step (a) of claim 43 in several instances: see abstract where it discusses a reactive molecule (i.e. Fluorescent label) able to donate fluorescent energy to said DNA duplex binding agent and therefore, the DNA duplex binding agent is capable of absorbing fluorescent energy and pg.7, lines 1-5 where it discusses the reactive molecule able to donate fluorescence to the dye (i.e. it is the donor molecule) and fluorescence is measured from the donor as it states, "emission from the donor molecule is reduced as a result of FRET and this reduction may be detected." Although it states that fluorescence of the dye is increased more than would be expected in this embodiment, the method relies on measuring the donor's emissions and therefore the acceptor (the dye) is not detectable in the context of the method (as explained in Claim Interpretation). This is further supported on pg.11 where it states "Preferably, the molecules used as donor and/or acceptor produce sharp peaks, and there is little or no overlap in the wavelengths of emission. Under these circumstances, it may not be necessary to resolve the strand specific peak from the DNA duplex binding agent signal. A simple measurement of the strand specific signal alone (i.e. that provided by the reactive molecule *[i.e. the fluorescent label]*) will provide information regarding the extent of the FRET caused by the target reaction" (see pg.11, lines 11-22). Lee explains further that ethidium bromide and fluorescein combination may fulfill this requirement and the reaction is quantifiable by reduction in fluorescence from fluorescein, expressed as 1/fluorescence. Thus, the emissions of the acceptor, the DNA Duplex binding agent (i.e. ethidium bromide) is not detectable in the context of the method). Lee teaches steps (b-d) of claim 43, see abstract, steps (b-d), for example.

Additionally see page pg.11, lines 11-22, for step (d) of monitoring fluorescence from the fluorescent label.).

Regarding claim 44, Lee teaches DNA duplex binding agents having a fused conjugated ring system (i.e. EtBr).

Regarding claim 48, Lee teaches the method according to claim 43 wherein the target nucleic acid is rendered single stranded prior to hybridization to the probe in step (c) (pg.8, lines 4-8).

Regarding claim 49, Lee teaches the method wherein the amplification reaction is the polymerase chain reaction (PCR) (pg.8, lines 21-23).

Regarding claim 50 and 51, Lee teaches the method wherein the probe hybridizes with the target nucleic acid during every cycle of the amplification reaction and wherein the fluorescence from the sample is monitored throughout the amplification reaction (pg.8, lines 30-38; pg.9, lines 1-14).

Regarding claim 52 and 53, Lee teaches the method wherein fluorescence data generated is used to determine the rates of probe hybridization and where the fluorescence data is used to quantitate the amount of target nucleic acid present in the sample (pg.9, lines 25-38; pg.10, lines 1-17).

Regarding claims 54-55, Lee teaches the method wherein the fluorescent label is a rhodamine dye, Cy5, fluorescein or a fluorescein derivative and wherein the fluorescent label is attached at an end region of the probe (pg.10, lines 28-37).

Regarding claim 56, Lee teaches the method wherein the fluorescent label is attached at the 3'end of the probe and prevents extension thereof by a polymerase (pg.10, lines 28-34; and pg.12, lines 30-34).

Regarding claim 57, Lee teaches the method wherein the probe is designed such that it is released intact from the target sequence during a phase of the amplification process other than the extension phase (pg.12, lines 15-30).

Regarding claim 58, Lee teaches the method wherein the probe is released intact from the target sequence during the extension phase of the amplification process by the action of the polymerase, and the amplification reaction is effected using a polymerase which lacks 5'-3' exonuclease activity (pg.12, lines 15-30).

Regarding claim 59, Lee teaches a method according to claim 43 which comprises performing nucleic acid amplification on a target polynucleotide in the presence of (a) a nucleic acid polymerase (b) at least one primer capable of hybridizing to said target polynucleotide, (c) an oligonucleotide probe which is capable of binding to said target polynucleotide sequence and which contains a fluorescent label (for steps (a-c) see abstract and pg.13, lines 34-35) and (d) a DNA duplex binding agent which is capable of absorbing fluorescent energy from the said fluorescent label, wherein emissions of the DNA duplex binding agent are not detectable in the context of the method; and monitoring changes in fluorescence during the amplification reaction (see abstract and Lee's teachings under claim 43 for DNA duplex binding acceptor characteristics and fluorescence label measurement for detection).

Regarding claim 60, Lee teaches the method wherein the amplification is suitably carried out using a pair of amplification primers (pg.13, lines 34-35).

Regarding claim 61, Lee teaches the method wherein the nucleic acid polymerase is a thermostable polymerase (pg.14, lines 1-2).

Regarding claims 62-65, Lee teaches the method wherein in a further step, a hybridisation assay is carried out and a hybridization condition which is characteristic of the sequence is measured [i.e. claim 62], wherein the condition is temperature, electrochemical potential, or reaction with an enzyme or chemical [i.e. claim 63-64], and wherein the method is used to detect allelic variation or a polymorphism in a target sequence [i.e. claim 65] (see abstract; pg.14, lines 34-37; pg.15, lines 1-31).

Regarding claim 66, Lee teaches a method comprising a) adding to a sample suspected of containing said sequence, a fluorescently labeled probe specific for said target sequence and a DNA duplex binding agent able to absorb fluorescence from a fluorescent label on the probe wherein emissions from the DNA duplex binding agent are not detectable in the context of the method (see abstract, pg.7, lines 1-5, pg.11, lines 11-22), (b) subjecting said sample to conditions under which the said probe hybridizes to the target sequence (see abstract, step (c)), (c) monitoring fluorescence from said sample and determining a particular reaction condition, characteristic of said sequence, at which fluorescence changes as a result of the hybridization of the probe to the sample or destabilization of the duplex formed between the probe and the target nucleic acid sequence (see pg.14, lines 34-37; pg.15, lines 1-31; pg.17, lines 4-21 for reaction conditions).

Regarding claims 67-69, Lee teaches a method wherein the reaction condition characteristic of said sequence is temperature, electrochemical potential, or reaction with an enzyme or chemical, and wherein the results obtained from two sequences are compared in order to determine the presence of polymorphisms or variations therebetween (pg.14, lines 34-37; pg.15, lines 1-31).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 5,491,063) in view of Smith et al., "Mitoxantrone-DNA binding and the induction

of Topoisomerase II associated DNA Damage in Multi-drug resistant small cell lung cancer cells," Biochem. Pharma. 1990, Vol.40, No.9, pp.2069-2078.

The teachings of the primary reference are discussed above. This reference does not teach the method where the DNA duplex binding agent is mitoxantrone.

However, the DNA duplex binding agent, mitoxantrone, was well known in the art at the time of the invention for use in fluorometric assays where donors and acceptors are used, as demonstrated by Smith. Smith et al. demonstrate through a flow cytometric assay that mitoxantrone is able to quench fluorescence from Ho33342 dye labeled cells (see Figure 7a and b; pg.2071, "Flow cyotmetric analysis of mitoxantron-DNA interaction by Ho33342-DNA," and pg.2075, left column). Although Smith is silent to the emissions of Mitoxantrone, Mitoxantrone is a compound having the formula of formula (I) and therefore, it inherently possesses the properties of such a formula (i.e. it inherently does not emit visible light).

One of ordinary skill in the art would have been motivated to modify the method of Fisher et al. to use a DNA duplex binding agent which does not emit visible light because Smith demonstrates that it was conventional in the art at the time of the invention to use of mitoxantrone as a DNA intercalator and a fluorescence quencher, where it inherently does not emit visible light. Since Lee demonstrates the benefits of using DNA duplex binding agents (as acceptors) that do not have emissions which are detectable in the context of the method, and Smith demonstrates the benefits of using mitoxantrone as a DNA duplex binding agent and fluorescence quencher, it would have been obvious to one skilled in the art to substitute one DNA duplex binding agent for the

other to achieve the predictable result of being able to measure emissions from only one label (i.e. the donor) and reduce background during the assay.

17. Claims 45-47, 70, and 85-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (WO/99/28500, of record) in view of Smith et al., "Mitoxantrone-DNA binding and the induction of Topoisomerase II associated DNA Damage in Multi-drug resistant small cell lung cancer cells," Biochem. Pharma. 1990, Vol.40, No.9, pp.2069-2078.

The teachings of the primary reference are discussed above. This reference does not teach the method where the DNA duplex binding reagent does not emit visible light [claim 85-86], is mitoxantrone or its salt, or nogalamycin or daunomycin [claim 45-46, 70]; or is a compound having the formula according to claim 47 [claim 47, 71].

However, the use of DNA duplex binding agents having the formula of formula (I), or more specifically, mitoxantrone, in fluorometric assays where donors and acceptors are used was well known in the art at the time of the invention, as demonstrated by Smith. Smith et al. demonstrate through a flow cytometric assay that mitoxantrone is able to quench fluorescence from Ho33342 dye labeled cells (see Figure 7a and b; pg.2071, "Flow cyotmetric analysis of mitoxantron-DNA interaction by Ho33342-DNA," and pg.2075, left column). Although Smith is silent to the emissions of Mitoxantrone, Mitoxantrone is a compound having the formula of formula (I) and therefore, it inherently possesses the properties of such a formula (i.e. it inherently does not emit visible light).

. One of ordinary skill in the art would have been motivated to modify the method of Lee et al. to use a DNA duplex binding agent represented by formula (I), or specifically, mitoxantrone, which does not emit visible light because Smith demonstrates that it was conventional in the art at the time of the invention to use mitoxantrone as a DNA intercalator and a fluorescence quencher, where it inherently does not emit visible light. Since Lee demonstrates the benefits of using DNA duplex binding agents (as acceptors) that do not have emissions which are detectable in the context of the method, and Smith demonstrates the benefits of using mitoxantrone as a DNA duplex binding agent and fluorescence quencher, it would have been obvious to one skilled in the art to substitute one DNA duplex binding agent for the other to achieve the predictable result of being able to measure emissions from only one label (i.e. the donor) and reduce background during the assay.

18. Claims 56-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fisher et al. (US 5,491,063) in view of Lee et al. (WO/99/28500, of record).

The teachings of Fisher are discussed above. Fisher does not discuss the method where the fluorescent label is attached at the 3' end of the probe, or where the probe is designed such that it is released intact from the target sequence during amplification, or where amplification is effected using a polymerase which lacks 5' to 3' exonuclease activity.

However, amplification using probes which comprise labels on their 3' end, which are designed to be released intact at various stages during amplification using polymerases which lack 5' to 3' exonuclease activity was conventional in the art at the

time of the invention, as demonstrated by Lee et al. (see above for the teachings of Lee et al.). Therefore, it would have been obvious to one of skill in the art to modify the method of Fisher et al. to use a probe with the label on the 3' end that is designed to be released intact during various stages in amplification, as well as use a polymerase which lacks 5' to 3' exonuclease activity because Lee et al. demonstrates that such practice was conventional in the art and further states that, "the position of the reactive molecule [i.e. fluorescent label] along the probe is *immaterial* although [in] general, they will be positioned at an end region of the probe" (pg.10, lines 31-34, emphasis added). As such, the skilled artisan would have had a reasonable expectation of success in using a probe where the label was positioned at the 3' end and was designed to remain intact when released during various phases in amplification while using a polymerase which lacks 5' to 3' exonuclease activity in the method of Fisher et al. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and include the claimed probe modifications and polymerase therein.

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 43-70 and 85-86 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-9, 11-13 are of U.S. Patent No. 6,833,257 in view of Smith et al., "Mitoxantrone-DNA binding and the induction of Topoisomerase II associated DNA Damage in Multi-drug resistant small cell lung cancer cells," Biochem. Pharma. 1990, Vol.40, No.9, pp.2069-2078. Although the conflicting claims are not identical, they are not patentably distinct from each other because of a genus: species relationship. For instance, Claim 1 of the '257 patent recites:

"A method for detecting the presence of a target nucleic acid sequence in a sample, said method comprising: (a) adding to a sample suspected of containing said nucleic acid sequence, a DNA duplex binding agent, and a probe specific for said target sequence, said probe comprising a reactive molecule able to absorb fluorescence from or donate fluorescent energy to said DNA duplex binding agent, wherein the 3' end of the probe is blocked to inhibit extension thereof during the extension phase, (b) subjecting the thus formed mixture to an amplification reaction in which the target nucleic acid is amplified, (c) subjecting said sample to conditions under which the said

probe hybridizes to the target sequence, and subsequently releasing said probe intact from the target sequence, and (d) monitoring fluorescence from said sample associated with one or both of the hybridization of the probe to the target sequence and the dissociation of the probe from the target sequence."

While the claim of the '257 patent is drawn to a method where the energy is donated to the DNA duplex binding agent, and the specification is drawn to DNA duplex binding agents which have a fused conjugated ring system (i.e. ethidium bromide) where said agents' emissions are not detectable in the context of the method, it does not specifically discuss those which do not emit visible light.

However, the use of DNA duplex binding agents having the formula of formula (I), or more specifically, mitoxantrone, in fluorometric assays where donors and acceptors are used was well known in the art at the time of the invention, as demonstrated by Smith. Smith et al. demonstrate through a flow cytometric assay that mitoxantrone is able to quench fluorescence from Ho33342 dye labeled cells (see Figure 7a and b; pg.2071, "Flow cyotmetric analysis of mitoxantron-DNA interaction by Ho33342-DNA," and pg.2075, left column). Although Smith is silent to the emissions of Mitoxantrone, Mitoxantrone is a compound having the formula of formula (I) and therefore, it inherently possesses the properties of such a formula (i.e. it inherently does not emit visible light). As such, it would have been obvious to substitute one DNA duplex binding agent for the other to achieve the predictable result of being able to measure emissions from only one label (i.e. the donor) and reduce background during the assay.

Summary

21. This Office Action is Non-Final.

22. No claims are free of the prior art.

23. Any remaining rejections and/or objections not addressed above are withdrawn in view of the amendments and/or arguments.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Molly E Baughman/
Examiner, Art Unit 1637

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
February 19, 2009